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REMARKS:

MMT SUBMISSION OF COMMENTS TO EPA ON AUGUST 23 COMMENTS BY ETHYL CORPORATION ON THE PROPOSED WAIVER FOR ADDITION OF MMT TO UNLEASED GASOLINE.

FOR PROBLEMS REGARDING TRANSMISSION, PLEASE CALL:

NAME: PHONE: ( )

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October 12, 1990

To: U. S. Environmental Protection Agency (EPA) Air Docket

From: National Institute of Environmental Health Sciences (NIEHS)

The following comments are submitted by the National Institute of Environmental Health Sciences to the Air Docket, EPA in response to "Supplemental Reply of Ethyl Corporation to Late-Filed Comments on Public Health Effects of HITEC 3000" submitted by Ethyl Corporation dated August 23, 1990. The following information is provided in response to Ethyl Corporation's (Ethyl's) analysis of the NIEHS comments filed with the Air Docket on the Ethyl Corporation's request for waiver to add methylcyclopentadienyl manganese tricarbonyl (MMT) to unleaded gasoline.

Our responses to the Ethyl's comments of August 23 fall into the following general areas:

* Estimates of environmental exposure and dose of manganese that reaches groups in the United States population.

* Speculation on the effect on public health that could be anticipated if the waiver application for addition of MMT to unleaded gasoline is granted.

* Discussion of the neurotoxicity of manganese.

* The need for determination of mass balance for manganese coming from MMT added to unleaded gasoline.

Estimates of Environmental Exposures to Manganese and Transfer of Manganese from the Environment to Humans

The NIEHS takes the position that the EPA has established a number of techniques for estimating exposures to environmental pollutants including manganese from use of MMT. It is NIEHS's view that this is the purview of the EPA. The EPA has developed their own exposure models. The NIEHS comments addressed the limitations of data on manganese exposures associated with adverse neurological and behavioral effects following manganese exposure. Such information is particularly needed for exposures that reflect doses under those encountered in occupational settings, i.e. including the range of 0.1 to 1.0 ug Mn/cubic meter of air.

Speculation Concerning the Nature and Extent of Adverse Health Effects that May Occur if the Waiver Request is Granted.

The NIEHS considers it reasonable to anticipate an increased risk of adverse effects of manganese associated with increasing exposure to manganese. The NIEHS considers it reasonable public health policy to anticipate the potential for adverse health consequences if a recognized human, neurotoxic agent such as MMT is approved for addition to a product (e.g., unleaded gasoline) that is widely dispersed both geographically and environmentally.

Ethyl Corporation has presented a number of assertions that addition of MMT to unleaded gasoline does not carry an inappropriately high risk of adverse consequences to the health of Americans. A direct example of such assertions may be noted in the letter from Roth Associates that states (on page 5, lines 4 through 6): "Thus we conclude, as in our earlier report, that the public health will not be adversely affected by increased manganese from MMT use." Additional examples of such assertions by Ethyl Corporation include the following:

> page 4, lines 8 through 20; page 5, lines 21 thrugh 25; page 6, lines 13 through 18; page 7, lines 1 and 2; page 8, lines 1 through 2 and 14 through 19 and 22 through 26; page 9, lines 1 through 15; page 11, lines 7 through 9; page 12 lines 1 through 3; page 14, lines 19 through 23; page 17, lines 5 through 8; page 25, lines 2 through 15. In the letter from Roth Associates, page 2, lines 31 through 36.

Although these statements have been made by Ethyl Corporation and/or their consultants, the NIEHS believes that for such assertions to be accepted or rejected additional analyses by scientific experts from a broad organizational base are needed. The NIEHS recognizes that there is also a need for additional data from well-conducted, state-of-the-art investigation that evaluates the continuum of neurotoxicity produced by MMT combustion products in an appropriate species of nonhuman primates.

Discussion of the Neurotoxicity of Manganese

There is scientific consensus that manganese exposure can produce human neurotoxicity. Although the Ethyl Corporation does not appear to dispute this fact, they have asserted that only quantities of manganese associated with occupational exposures produce clinical signs and symptoms of extrapyramidal tract

dysfunction, called "manganism" which bears close clinical resemblance to, but is not identical with, Parkinson's disease. In the view of NIEHS the fundamental issue is not the doses of manganese needed to produce overt manganism. Rather, the fundamental issue is whether or not additional manganese exposure that would occur with the addition of MMT to unleaded gasoline would increase the risk of neurotoxicity and/or reduction in the reserve function of the nervous system of the United States population.

The NIEHS view is that adequate studies in an appropriate species (e.g., nonhuman primates) are needed to assess the continuum of neurotoxic effects produced by manganese and the combustion products of MMT at appropriate doses and during appropriate developmental periods. To date, the studies of manganese have not included subtle indices of neurobehavioral response as have been conducted, for example, with lead. To assert that neurotoxic effects do not occur at manganese exposures lower than those that produce overt signs and symptoms of neurological disease does not reflect scientific experience with neurotoxic agents.

As noted by Roth Associates (page 3 through first paragraph of page 5), the NIEHS has cited three epidemiological studies that have reported neurological signs and symptoms associated with manganism, but without full parkinsonian syndrome: Ferraz et al. (1988), Sano et al., (1982); and Szeliga-Cetnarska (1987). Epidemiological studies do not prove causality; however, they can assess association. When data from epidemiological studies that report association between the agent (e.g., manganese) and the response are biologically plausable, the argument for causality is strengthened. Such biological plausibility includes appearance of signs and symptoms consistent with reports of clinically overt toxicity in highly exposed human and with nonhuman primate models of neurological effects following manganese exposure.

* Ferraz et al. (1988) reported rigidity as a feature present in the Maneb (manganese ethylene-bis-dithiocarbamate) exposed worker group. Rigidity is one of the characteristic features of clinical manganism.

* Sano et al. (1982) reported increased neurological symptoms among a group of manganese mine workers and ore grinders as compared to a control group. Many workers did not have the full clinical parkinsonian syndrome, however, they had some signs and symptoms of the disease. Ethyl Corporation asserts that their exposures were "many orders of magnitude higher than would be

associated with MMT use." (page 4, Roth Associates). The NIEHS notes that the range of manganese exposures that produce neurological effects is not known and that the Roth Associates statement is speculative.

* The report by Szeliga-Cetnarska (1987, English abstract only, full text in Polish) identifies reduced conduction in motor and sensory nerve fibers of manganese-exposed workers. Roth Associates comment that it is not clear if the workers were exposed to toxic substances other than manganese. This issue frequently can be raised in epidemiological studies, however, that is the reason a control group is used.

The Roth Associates letter (pages 5 through 7) addresses the issue of mechanisms of neurotoxicity produced by manganese. NIEHS pointed out that because substantial depletion of neurotransmitters and other neurochemicals can occur prior to the onset of clinical signs and symptoms, absence of overt effect does not mean an absence of damage produced by manganese exposure. The NIEHS stands by the possibility that manganese can cause "silent" neurological damage at doses lower than those that produce overt signs and symptoms of manganese intoxication. In addition to the literature cited in the July 23 submission of the NIEHS to the EPA Air Docket, additional literature supports this position. Among other reviews is that of Seeman and Niznik (1990). These investigators note that in Parkinsonian syndrome the number of dopamine-containing cell bodies in the substantia nigra is reduced by 60-86% of age-matched control tissues, and that the loss of dopamine in the nerve terminals in the striatum is even greater, amounting to a 90-99% loss in the putamen and a 58-95% loss in the caudate nucleus. Thus, clinical manifestations of parkinsonism are not present until substantial and irreversible cell loss has already occurred.

Roth Associates has indicated that in their opinion that reviews on Parkinson's disease have no relevance to manganese toxicity. However, this notion cannot be fully supported after reading the reference (Bleecker, 1988) cited by Roth Associates. Bleecker does not refute that manganese exposure produces severe neurotoxicity but prefers to use parkinsonism rather than the specific "Parkinson's disease". The following quote comes from the end of her review (Bleecker, page 477, 1988) and makes this point and raises the concern that the effects of neurotoxins may be greater in the aged nervous system:

"In summary, parkinsonism may be a clinical marker of exposure to a neurotoxin but is associated with a variety of neuropathological mechanisms. Also, as mentioned, the aged nervous system provides a substrate which has less regenerative

abilities and therefore may express irreversible pathology earlier and at lower doses. Future research focusing on the interaction between age-related changes in the nervous system and the biologic effects of neurotoxins may prove to be fruitful in defining the underlying mechanisms producing Parkinson disease."

Variability in the signs and symptoms of neurological disease associated with manganese exposure can be noted in the report of Eriksson et al. (1987) cited by Roth Associates. Eriksson et al. (1987) investigated the effects on manganese oxide on monkeys (Macaca fascicularis) on the neurological symptoms produced by subcutaneous injection over a 5 month period of 8 grams of manganese as oxide. These effects were evaluated for a period of up to six months after the last injection of manganese. All four of the manganese-exposed monkeys developed adverse behavioral and severe neurological symptoms including unsteady gait and clumbsiness of the hands and feet. The two monkeys observed for six months developed an action tremor, while the two monkeys with behavioral and motor effects that were sacrificed after five months had not developed tremor. This illustrates that exposure period can influence which signs and symptoms are observed in a particular experimental model.

Likewise, the limited data base on neurobehavioral effects of manganese exposure may be a factor in the inconsistencies noted between studies. The literature is not fully consistent in describing the specific site of greatest histological and neurochemical change within the nervous system following manganese exposure. Examples include reports of manganese neurotoxicity for both nonhuman primates (Erikson et al., 1987; Pentschew et al., 1963; Ulrich et al., 1979) and in human autopsy tissues (e.g., Bernheimer et al., 1973; Yamada et al., 1986). Although the reasons for this variation are not known at this time, there is substantial, irrefutable evidence that manganese produces a clinical syndrome that includes severe disorders of gait and movement. What is not yet known is the shape and range of the human dose-response curve that relates manganese exposure to the development of human signs and symptoms of "manganism". Because of the relatively crude nature of the clinical end-points of neurological function used to date, it is not possible to exclude preclinical changes in neurological, behavioral, or developmental processes.

Roth Associates state (page 6, lines 34 through 38) that "There is little experimental evidence available in support of the hypothesis that exposure to manganese at concentrations below those that cause overt signs and symptoms of neurological disease damages neurons or potentiates other neuronal disorders." The

NIEHS has previously stated that there is a serious need for additional experimental evidence in appropriate primate models evaluating the continuum of manganese-induced neurotoxicity. The absence of evidence for a condition that includes irreversible neurotoxicity should not be a reason for permiting addition of a neurotoxic agent to a substances (i.e., unleaded gasoline) that is geographically and environmentally widely dispersed.

With regard to the limited data base on association of manganese with learning disabilities, the NIEHS accepts that this data base is provisional. The NIEHS notes that several of the earlier papers that associated lead with learning disability and hyperkinesis were methodologically imperfect. However, following several longitudinal, prospective epidemiological studies (among others see Bellinger et al., 1987; Dietrich et al., 1987; McMichaels et al., 1988) intellectual deficits produced by relatively low-level lead exposures have been demonstrated. Adequate investigation of manganese associated learning deficits are needed to evaluate this issue.

Roth Associates address the question of the relative toxicity of Mn3O4 as compared with other manganese compounds. The NIEHS points out that the American Conference of Government and Industrial Hygienists (ACGIH) has a lower TLV for manganese tetroxide than for manganese. Their 1988 update lists the TLV-TWA for manganese and compounds as 5 mg/m3, but indicates that the TLV-TWA for manganese tetroxide (Mn3O4) is 1 mg/m3 (ACGIH, 1988).

Exposure to the Additive

In its previous communication the NIEHS has cited data showing a nasal olfactory pathway for metal access into the nervous system (Perl and Good, 1988). This is a potential route of exposure to the additive that has not been previously considered.

The Need to Conduct a Study of Mass Balance for Managanese

The NIEHS considers that it is not at all clear how the ambient concentration levels of 0.1 ug/m3 were determined because no details were given. The NIEHS also considers this to be a major flaw with this application because it does not make it possible to estimate lung dosimetry to manganese exhause emissions. In this memorandum, the NIEHS also notes that the claim that MMT use reduces exhaust emissions of CO, NOx, benzene, formaldehyde etc., is unlikely. These emissions are not reduced because of

MMT; rather, this reduction is most probably due to the catalytic converter. Exhaust emission profiles with and without MMT should be supplied.

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October 25, 1990

BY MESSENGER

Ms. Mary T. Smith
Director
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EN-397F
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401 M Street, S.W.
Washington, D.C. 20460

Public Docket No. A-90-16

Dear Ms. Smith:

In comments filed with EPA on October 19, 1990, Ethyl specifically addressed two questions which arose during recent meetings with EPA officials concerning Ethyl Corporation's ("Ethyl") waiver application for use of HiTEC® 3000 ("the Additive") in unleaded gasoline. In this letter, Ethyl provides additional information relevant to one of those questions -- whether the inhalation of manganese presents risks to public-health different and more serious than those associated with the ingestion of manganese.

Enclosed for your review is a description of a model for predicting the relative share of blood manganese levels attributable to inhaled versus ingested manganese at various average ambient manganese concentrations. The model is based on human blood and circulation data, and assumptions regarding the body's absorption and excretion mechanisms governing manganese.

Application of this model shows that the contribution of inhaled manganese resulting from use of the Additive to levels of manganese in the blood would be very small. Assuming an average ambient manganese level of 0.1 ug/m3 -- a level approximately two times higher than Ethyl's worst-case prediction -- the contribution of inhaled manganese to total manganese levels in blood would be less than one percent. Under a more realistic average ambient manganese level of 0.05 ug/m3, the contribution

of inhaled manganese to blood manganese levels drops to 0.5 percent or less. This analysis demonstrates that the overwhelming source of manganese in blood, and therefore the manganese transported to the brain and other internal organs would continue to be ingested manganese even if the Additive were present in unleaded gasoline.

Sincerely,

John J. Adams
F. William Brownell
Kevin L. Fast

Enclosure

cc: Public Docket No. A-90-16
William G. Rosenberg, Esq.
Erich W. Bretthauer
Dr. J. Clarence Davies

Health Effects of Manganese in the Air

By: Ben F. Fort, Jr.
Nancy A. O'Malley

The major pathway for manganese entrance to the body is absorption in the intestines from food and water. The only other significant pathway for manganese to enter the body is from inhalation of air containing manganese particulates. However, even before considering absorption differences, the amount of manganese inhaled with air is normally much smaller than the amount taken into the gut.

A. Sources of Manganese

1. Gut Absorption of Manganese

Absorption of manganese from the human gut has been estimated by Mena et al., 1969, as 3% of oral intake for healthy subjects and 4% for manganese miners with chronic manganism. These values appear true for other mammalian species (Pollack et al., 1965).

Dietary manganese intake has been estimated as follows (EPA HAD, 1984):

Group	Average daily intake milligrams	Reference
Adults, college women	3.7 mg	North et al., 1960
Adults	2.3-2.4	Schroeder, 1966
Adults, male	3.3-5.5	Tipton, 1969
Adolescent males (15-18 years)	3.8	US FDA, 1978
Calculated average	3.05 mg	

2. Lung Absorption

The degree of absorption of manganese from a human inhalation exposure is highly dependent upon particle size. Site of deposition and time of clearance from the site can be thought of as follows:

>10-15 um: deposited outside the thorax, insolubles cleared to esophagus and swallowed in minutes

4-10 um: 50% are deposited in the tracheobronchial tree, and are cleared on the order of hours

2-4 um: 25-65% deposited in alveoli, insolubles cleared in weeks, months, years

< 2 um:
a. 50-80% can remain suspended and be exhaled
b. Conservatively, none could be exhaled, 80% deposited alveolarly, insolubles cleared weeks, months, years

Thus, particulates deposited outside the thorax and in the tracheobronchial tree would be cleared to the gastrointestinal tract, and would be absorbed similar to dietary manganese. Dissolution of particulates in the alveoli could allow manganese to be absorbed into the lung circulation directly. Indirectly, particles could be transported to the regional lymph nodes, where dissolution could release manganese to the lymph or blood circulation. Studies of retention in man and animals have shown rapid clearance of the nasopharyngeal and tracheobronchial region, and clearance of the alveolar region dominated by the solubility of the material (Hobbs and McClellan, 1986).

The EPA in it's "Health Assessment Document for Manganese", 1984, used ambient air sampling data (NASN) to estimate human exposure by inhalation at different concentrations of air manganese. They used the air monitoring data by making the assumption that the fine fraction of particles in the air samplers would reflect particles deposited 100% in the alveoli, and the coarse fraction would represent that deposited 100% in the tracheobronchial tree. Very large particles were excluded from the samplers, and thus did not enter into their estimates. Total thoracic exposure would be particles deposited in the alveoli and in the tracheobronchial tree.

The following exposure estimates were made by the EPA for a 70 kg man breathing 20 cubic meters (m^3) of air per day:

NASN data used	Concentration (ug/m^3)	Total inhaled Mn, ug/day*	Site Deposited	Exposure (ug/day)
1982 avg.	.023	.460		
			alveolus	.072
			total thoracic	.26
1982 high	.661	13.22		
			alveolus	6.6
			total thoracic	10.0
1960 high	10	200.00		
			alveolus	100
			total thoracic	152

(From EPA HAD, 1984 except for * which was calculated from air concentration)

(Tracheobronchial manganese = Total thoracic - alveolar manganese)

B. Possible differences in inhaled versus ingested manganese

There has been speculation that manganese in the blood resulting from lung absorption might increase significantly before it is regulated by the body control mechanisms for manganese coming from dietary sources. This is based on possible differences in elimination mechanisms for manganese in the blood originating from lung or from gut absorption. Manganese absorbed via the gut into venous blood flows through the liver where the liver elimination mechanisms regulate the blood concentration before circulation to other body tissue and organs. Manganese absorbed into blood in the lung enters arterial blood directly and is circulated to body tissue and organs. Only about 21% of the total venous blood flows through the liver each blood flow cycle. The 79% venous blood that does not pass through the liver is an internal loop which provides the possibility of buildup of lung-absorbed manganese.

C. Blood Flow Model

To examine the relationships of air and gut manganese to the circulating manganese levels, a simple model of body blood flow was constructed. The model is capable of evaluating the relative fractions of blood manganese originating from lung and gut absorption as the inhaled air manganese content varies. The fractions are evaluated at homeostatic-regulated total blood manganese content.

The complete blood flow system is depicted in Figure 1. All major body organs and systems are shown with the generally accepted percentages of total blood flow (Guyton, 1987; Ritschel, 1976). The major manganese inputs are absorption from the gut and lung represented in Figure 1 by the MnG and MnI variables, respectively. The minor input from skin absorption is not considered. Manganese is eliminated from the body in feces, bile, fingernails and toenails, urine and hair. The urine elimination route is thought to become active only after the liver route is overwhelmed. The bile and feces are the only routes of elimination considered in the model at this time.

The computations in the model are iterative with respect to air/gut ratio in the blood and liver elimination fraction. The air/gut ratio is a direct solution for fixed elimination fraction but was programmed as iterative to retain the generality of the solution technique. The homeostatic regulation of total blood manganese flow was achieved by iterative adjustment of the liver elimination fraction. This type model can be utilized for an enhanced model involving sources and/or sinks plus time dependent functions affecting these sources and/or sinks. The computed air/gut ratios for various levels of air concentrations will be discussed in Section E following.

D. Assumptions and Parameters for the Model

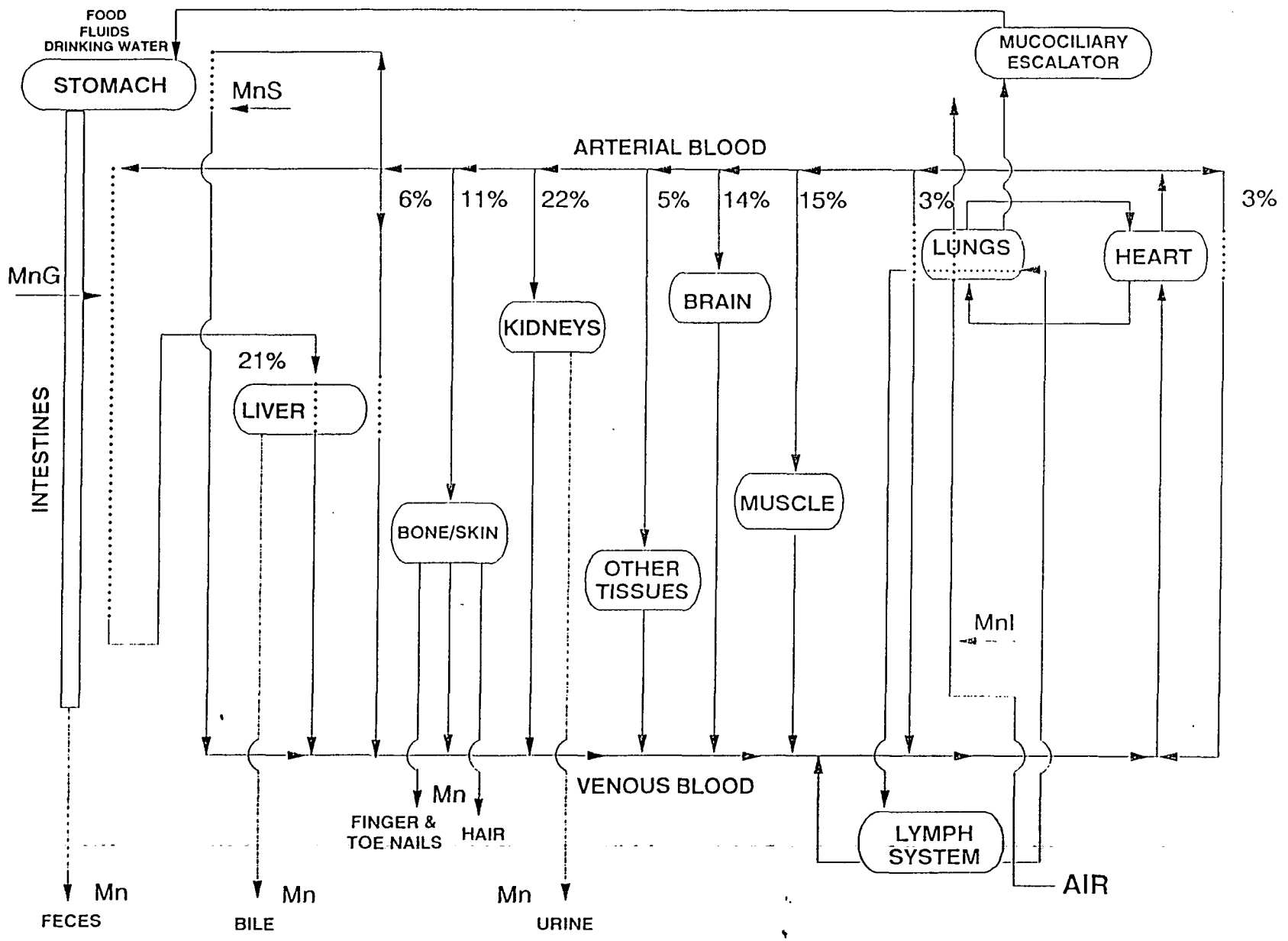
The model input parameters are based on human blood and circulation data. Blood manganese content from the literature exhibits a wide range of values. Factors altering blood values can include tissue fluid contamination in sampling whole blood, the analytical method used and the choice of anticoagulant. The EPA "Health Assessment Document for Manganese", 1984, states neutron activation and electrothermal atomic absorption analytic procedures have shown average normal concentrations of manganese in whole blood to be 0.7-1.2 ug/100 ml.

Our model assumed that the blood manganese levels would be tightly controlled by the body absorption and excretion mechanisms. This is supported by animal studies. Ulrich's study (1979) in which squirrel monkeys and rats were exposed continually by aerosol for 9 months to 11.6, 112.5 and 1152 ug Mn/m^3 with particles of 0.11 um diameter did not show significant elevations of blood manganese except at the highest exposure level.

Exposure Group (ug/m^3)	Rats (n=10) (ug/100 ml)	Monkeys (n=4) (ug/100 ml)
Control	1.15 +/- 0.46	1.10 +/- 0.17
11.6	1.30 +/- 0.55	1.30 +/- 0.13
112.5	1.75+/- 1.06	1.54 +/- 0.17
1152	2.43 +/- 0.88	5.67 +/- 1.28

Figure 1

Human Blood Flow System



As our model was going to consider concentrations well below 1152 ug/m^3, we assumed that blood concentrations would be controlled at steady state to preexposure values. For modelling, a blood concentration of 1.2 ug/100 ml was used. At a flow rate of 5000 ml/minute, a manganese flow of 60 ug/minute resulted and was assumed to originate from gut absorption.

Dietary intake has definite influence on manganese clearance rates. For example, Britton and Cotzias (1966) reported a two-component whole body clearance rate for manganese in mice. A 10 fold increase in dietary intake decreased the half time of the isotope by about 50%. Suzuki (1974) had similar findings in a study in mice receiving different levels of manganese in drinking water for 30 days before radiolabel. Whole body clearance was estimated to be 6 days for lowest concentration group (20 mg/l), and decreased to 3 days (100 mg/l) and 1 day (2000 mg/l). Our model can vary dietary intake values for manganese, but for the present discussion, dietary levels were kept at an average daily intake of 3.05 mg/day (EPA HAD, 1984).

A 70 kg man inhales approximately 20 cubic meters of air per day (EPA HAD, 1984). While all the manganese in this air would be inhaled, studies of particulate distribution show that only approximately 16% of it would be distributed such that it could be absorbed into the bloodstream (Yeh and Scham, 1980). Thus, the model initially used the assumption that 16% of inhaled manganese would be absorbed. (Sixteen per cent absorption of inhaled manganese is comparable to the absorption calculated from the estimated alveolar exposure of a 70 kg man at an air concentration of 0.023 ug/m^3 as developed in the EPA HAD, 1984. This is shown below.) The lung absorption was made variable in the model and can be increased or decreased to reflect changes in the overall absorptivity (particle distribution and solubility) of the inhaled manganese. (The same effect on blood levels could be realized by artificially increasing the air concentration.) Values of 50% lung absorption appear to fit the higher ambient air concentrations in the EPA exposure estimate.

NASN data used	Air levels (ug/m^3)	Mn in 20m^3 ug/day*	Alveolar exposure (ug/day)	Absorption*
1982 avg.	.023	.460	.072	16%
1982 high	.661	13.22	6.6	51%
1960 high	10	200.00	100	50%

(From EPA HAD, 1984 except for * which was calculated from air concentrations, and the alveolar absorption estimate)

By adjusting the manganese lung absorption variable in the 20 to 45 percent range, the model produces very comparable air/gut contribution to blood manganese ratios to those that can be derived from the data used for exposure estimates in the EPA HAD, 1984.

E. Comparison with estimates derived from the EPA Exposure Estimates

From the EPA estimates of exposure, the relative contribution of inhaled and ingested manganese to the circulating manganese can be approximated. Using the very conservative assumption that all manganese in the alveolus is absorbed into the blood during the day it is inhaled, and that tracheobronchial manganese would be carried to the esophagus and swallowed, the distribution of the inhaled manganese (from the same ambient air concentrations) would be:

Air concentration ug/m^3	Amt Mn into blood from Alveolus	Amt Mn into gut from Lung
.023	+ .072 ug/day	+ .188 ug
.661	+ 6.6 ug/day	+ 3.4 ug
10	+100 ug/day	+ 52 ug

Carrying the EPA estimates a step further, contributions to circulating manganese can be estimated from dietary intake. Daily ingested manganese averages 3.05 mg/day (average value for healthy adults, EPA, 1984). Tracheobronchial manganese is also delivered to the gut. Absorption of gut manganese is approximately 3% (EPA, 1984). The intake of manganese from the lung (alveolus) into the blood, and from the gut (diet and tracheobronchial) into the blood can be estimated as:

Air ug/m^3	Intake from lung	Intake from gut	Air/gut %	Air/Total Intake%
.023	.072 ug/day	91.51 ug	.079%	.078%
.661	6.6 ug/day	91.60 ug	7.2%	6.7%
10	100 ug/day	93.06 ug	107.4%	51.8%

Our blood flow model, using a blood manganese level of 1.2 ug/100 ml, the same 3.05 mg Mn in the diet, shows very similar air gut and air total ratios at steady state letting lung absorption vary from 20-45%, as shown below:

Air ug/m^3	Air/gut %	Air/Total Intake%
0.023	0.10-0.23% (.079% EPA)	0.10-0.23% (.078% EPA)
0.05	0.22-0.49%	0.22-0.49%
0.1	0.44-0.99%	0.44-0.98%
0.661	2.90-6.53% (7.2% EPA)	2.82-6.13% (6.7% EPA)
10	43.97-99.14% (107.4% EPA)	30.54-49.78% (51.8% EPA)

Note: Minimum value assumes 20% lung absorption.
Maximum value assumes 45% lung absorption.
EPA value is calculated from EPA HAD, 1984 data.

Similarly, the model was used to estimate air/ingestion contribution ratios using the Human Equivalent Exposure Levels (HEEL) estimated from animal data by the EPA, 1984. The HEEL values were derived from the no observed effect levels seen in two species of animals in an inhalation study by Ulrich et al., 1979. The no observed effect levels were 113 ug/m^3 for 9 months of continual exposure in rats and squirrel monkeys. Using size factors to estimate animal intake and making adjustments for human proportions, and applying a safety factor of 10 to the estimated human equivalent exposure level, the adjusted air concentrations were 5 and 8.7 ug/m^3 based on the rat and squirrel monkey data. The contribution ratios calculated by our model for this air concentration, using 45% absorption for inhaled manganese are as follows:

Air ug/m^3	Air/gut %	Air/Total Intake%
5	49.47%	33.10%
8.7	83.80%	46.30%

Note: Values assume 45% absorption
Air concentrations are Modified HEEL values, EPA HAD, 1984

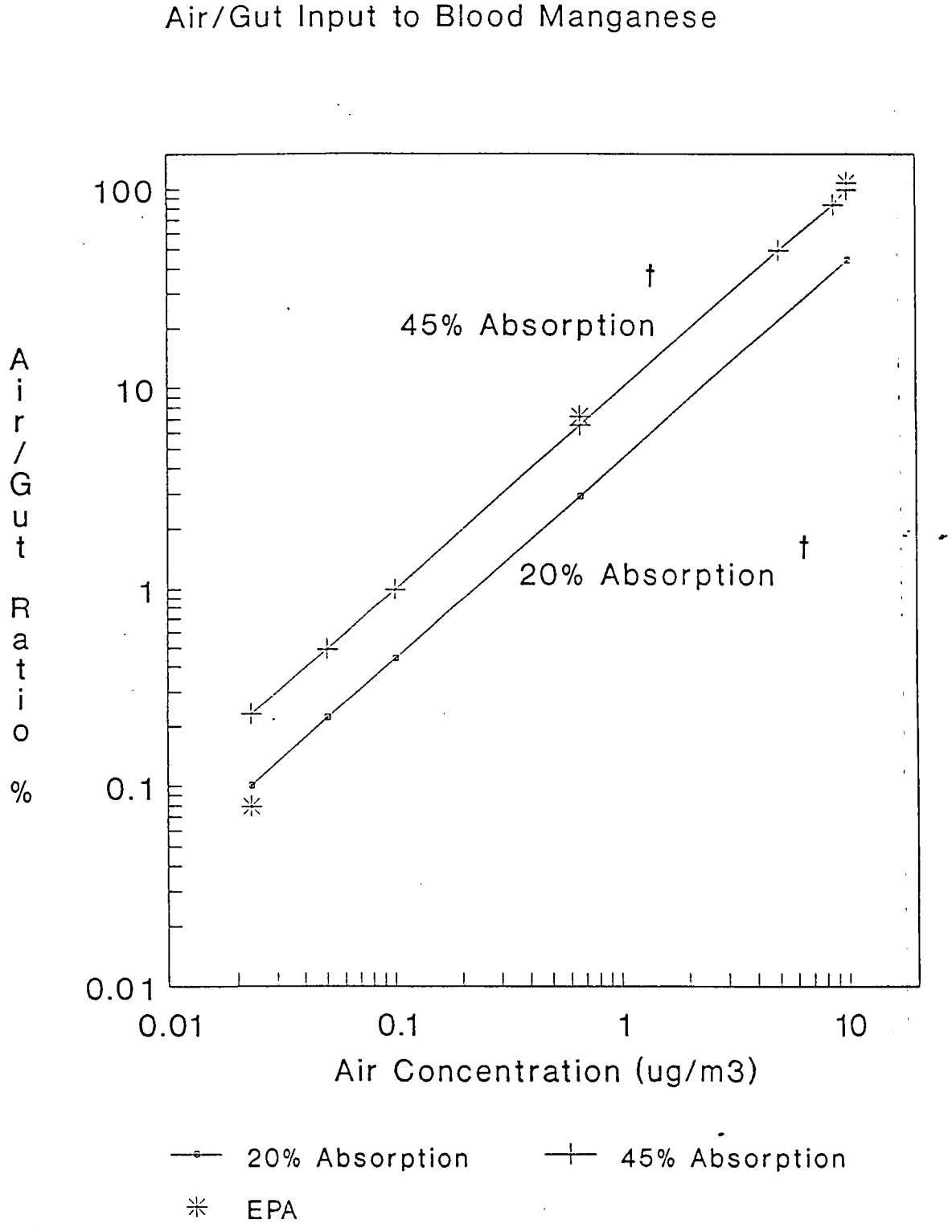
These results for air/gut ratios at different air concentrations are plotted in Figure 2. As has been mentioned, the model reasonably approximates the air/gut contributions to blood manganese at homeostasis derived from the EPA estimates of alveolar exposure at air concentrations that vary from 0.023 to 10 ug/m^3. Even assuming 45% lung absorption in our model (an absorption value that better fits very high air concentrations rather than the 16-20% that better fits low concentrations), the air/gut ratios for the air concentrations of concern (less than 0.1 ug/m^3) are 1% or less.

Based on this model, using a conservative assumption that 45% lung absorption of manganese from ambient air containing 0.1 ug/m^3 would occur and that dietary intake of manganese would be 3,050-3,500 ug/day (an average dietary intake to the recommended daily allowance, NRC, 1989), only 1% by weight of blood manganese would be attributable to inhaled manganese at steady state. If a more realistic average air concentration of manganese of 0.05 ug/m^3 is used, the amount of blood manganese attributable to inhalation drops to 0.5%.

Conclusions:

Based on calculations from this model, we conclude that at average current ambient air manganese concentrations -- and at maximum ambient manganese concentrations that will result from the proposed use of HiTEC® 3000 (conservatively predicted to be approximately 0.05 ug/m^3) -- manganese from inhalation constitutes less than one percent of the blood manganese. Air is therefore the source of less than 1% of the manganese reaching the brain at homeostasis. (In comparison, air/gut ratios of 49-84% would be seen at air concentrations that are the human equivalents of no effect exposures in animals.)

Figure 2



† Percentage of inhaled manganese which is absorbed.

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